Synthesis of Functionalized Pyridones via Palladium Catalyzed Cross Coupling Reactions

Jian-min Fu,* Yong Chen, Arlindo L. Castelhano*

Cadus Pharmaceutical Corp. 777 Old Saw Mill River Road, Tarrytown, New York, USA 10591-6705, USA

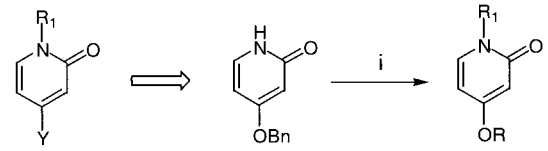
Fax (914) 467-3565; E-mail: jfu@cadus.com, acastelhano@cadus.com

Received 10 October 1998

Abstract: Convenient, palladium catalyzed cross coupling reaction conditions lead to novel N- and 4-substituted pyridones.

Among heteroaromatic compounds, substituted pyridones[1] have been found as important starting materials for the synthesis of more complex molecules.[2] The pyridone structure also appears in a number of natural products such as camptothecin,[3] and as a peptidomimetic element in enzyme inhibitors of elastase[4] and thrombin.[5] We have been particularly interested in introducing carbon-based substituents onto the pyridone ring in compounds designed for SH2 domains of tyrosine phosphatases and kinases, and compound libraries targeting G-protein coupled receptors. The pyridone N-substituent introduces an element of diversity or a site for further modification via library synthesis. In the specific case of the N-phosphonomethyl moiety, **4a,** (Scheme 1) this results in a phosphotyrosine mimetic,[6] a key component in ligands recognized by protein SH2 domains implicated in cancer, inflammation and allergy. Herein we report a very efficient synthesis for the assembly of N- and 4-substituted pyridones through palladium catalyzed cross coupling reactions of pyridone triflates **4a-c** with aryl boronic acids or the zinc reagent of β-iodoalanine. Coupling conditions are described that render pyridone triflates useful in reactions with a variety of aryl, heteroaryl, alkynyl, and alkyl coupling partners at or near room temperature.

The pyridone triflates were made by regiospecific N-alkylation of commercial O-benzylpyridone **1** with K_2CO_3 in acetonitrile (Scheme 1). Hydrogenolysis with Pd-C in methanol generated N-alkyl 4-hydroxypyridones **3a-c**. The formation of triflates **4a-c** occurred rapidly at -78°C with triflic anhydride and triethylamine.



(i) K_2CO_3, CH_3CN, R_1X, reflux, 2d
(ii) H_2, Pd-C, MeOH, rt, 2h
(iii) Et_3N, $(CF_3SO_2)_2O$, CH_2Cl_2, -78°C, 5 min

	R_1-X	Yield (%) 2	3	4
a	$BrCH_2P(O)(OPr^i)_2$	98	96	70
b	$BrCH_2COOBu^t$	86	86	67
c	$Cl(CH_2)_3COOMe$	68	100	67

Scheme 1

The palladium catalyzed cross coupling reaction has been widely used in organic synthesis for the construction of a variety of complex molecules.[7] Organo triflates have been reported to couple with tin,[8] boron,[9] zinc[10] and Grignard reagents.[11] Likewise, we successfully coupled the pyridone triflate **4** with aryl boronic acids and phenyl acetylene (Table 1). Although the Suzuki reaction is normally carried out at reflux temperatures, several groups have reported the coupling of organobromo and iodo reagents with aryl boronic acids at ambient temperature.[12] To our knowledge, the corresponding *non-aqueous* coupling between aryl triflates and boronic acids have not been reported.[13] Such conditions are preferred for robotic synthesis of compound libraries for drug screening. Indeed, we have found that the coupling of **4a** with 2-thienyl boronic acid proceeds at *room temperature* under the specific conditions of $Pd(PPh_3)_4/K_2CO_3$/THF-DMA (1:1) in a superior yield (96%) than the regular reflux conditions ($Pd(PPh_3)_4$/aq Na_2CO_3/DME), (entries 4 and 5, Table 1).

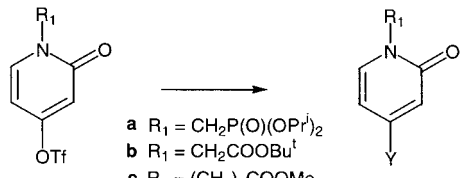
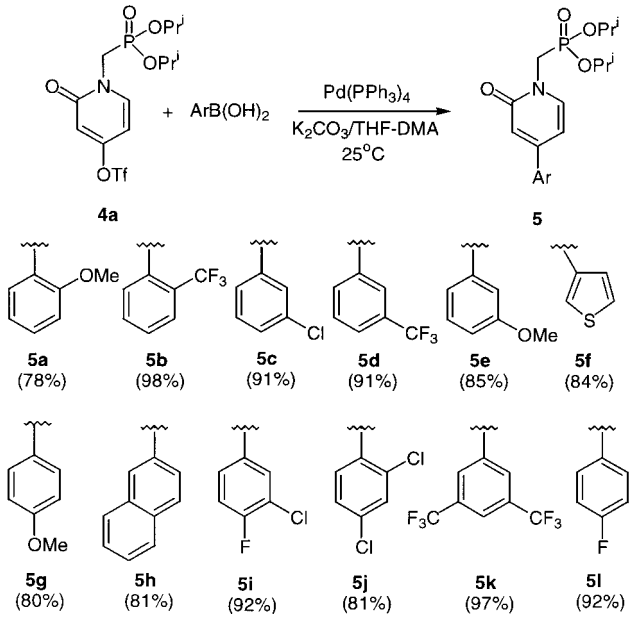


Table 1. Palladium catalyzed triflate coupling reactions

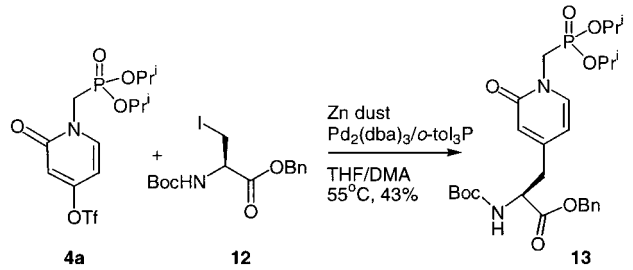
Entry	Y	Product	Catalyst	Reaction conditions	Yield (%)
1	Ph	**6a**	$Pd(PPh_3)_4$	90°C/aq Na_2CO_3/DME	64
2	2-MePh	**7a**	$Pd(PPh_3)_4$	90°C/aq Na_2CO_3/DME	91
3	3-NO_2Ph	**8a**	$Pd(PPh_3)_4$	90°C/aq Na_2CO_3/DME	81
4	2-thienyl	**9a**	$Pd(PPh_3)_4$	90°C/aq Na_2CO_3/DME	78
5	2-thienyl	**9a**	$Pd(PPh_3)_4$	25°C/K_2CO_3/THF-DMA	96
6	≡—Ph	**10b**	$PdCl_2(PPh_3)_2$	100°C/iPr_2NEt/DMF	94
7	≡—Ph	**11c**	$PdCl_2(PPh_3)_2$	100°C/iPr_2NEt/DMF	74

Subsequently, we applied these room temperature conditions to the coupling of **4a** with other boronic acids (Scheme 2). As a preamble to robotic synthesis, cross coupling reactions were carried out in 20ml borosilicated vials by mixing triflate **4a** with commercial boronic acids, palladium catalyst, and potassium carbonate in 1:1 ratio of THF and DMA. The mixture was shaken on a J-CHEM shaker for 48 h. To assure purity, the mixture was filtered and the crude product purified by preparative thin layer chromatography.[14] Monosubstituted phenyl boronic acids with electron donating and electron withdrawing groups at *otho-*, *meta-*, or *para* positions did not affect the outcome of the product. Disubstituted phenyl, naphthyl, and heteroaromatic boronic acids also gave excellent yields of coupled product. The isopropyl phosphonate esters were further hydrolyzed with iodotrimethylsilane and N,O-bis(trimethylsilyl)acetamide in acetonitrile, followed by TFA/CH_3CN/H_2O[15] to yield the corresponding phosphonic acids.[16]

The usefulness of the pyridone triflate intermediate **4a** is also evident with the coupling to β-iodoalanine to generate pyridone-based phosphotyrosine mimetics (Scheme 3). Previous reports of the coupling of halogen compounds with zinc reagents[17,18] prompted us to investigate the coupling of triflate **4a** with the zinc reagent generated *in situ* from the protected β-iodoalanine, **12**. After a considerable effort, the method of Jung[18b] using THF-DMA as the solvent system and $Pd_2(dba)_3$/*o*-tol_3P as the palladium catalyst,[19] provided the desired product **13**[20] in 43% isolated yield.



Scheme 2



Scheme 3

In summary, the N-alkyl, 4-pyridone triflate **4** is a versatile reagent for palladium catalyzed cross coupling reactions with phenyl acetylene (sp carbon) and aryl boronic acids (sp^2 carbon) at *room temperature*, and the zinc reagent of β-iodoalanine (sp^3 carbon).

Acknowledgements: We are indebted to Mr. Marcus Colucci for the LC-MS analysis of intermediates and target compounds. We thank Prof. S. Sieberth for helpful discussions and Prof. M. Jung for a preprint of ref. 18(b).

References and Notes

1. Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R. and Rees, C. W., Eds., Vol. 2, Pergamon Press, 1984.
2. (a) Comins, D. L.; Gao, J. *Tetrahedron Lett.* **1994**, *35*, 2819. (b) Sieburth, S. M.; Hiel, G.; Lin, C.-H.; Kuan, D. P.; *J. Org. Chem.* **1994**, *59*, 80. (c) Schmidhauser, J. C.; Khouri, F. F. *Tetrahedron Lett.* **1993**, *34*, 6685. (d) Sieburth, S. M.; Chen, J.-L. *J. Am. Chem. Soc.* **1991**, *113*, 8163.
3. For total synthesis of camptothecin using substituted pyridones as starting materials, see: (a) Comins, D. L.; Hong, H.; Saha, J. K.; Gao, J. *J. Org. Chem.* **1994**, *59*, 5120. (b) Comins, D. L.; Hong, H.; Gao, J. *Tetrahedron Lett.* **1994**, *35*, 5331. (c) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863.
4. (a) Beholz, L. G.; Benovsky, P.; Ward, D. L.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1997**, *62*, 1033. (b) Bernstein, P. R.; Gomes, B. C.; Kosmider, B. J.; Vacek, E. P.; Williams, J. C. *J. Med. Chem.* **1995**, *38*, 212.
5. Sanderson, P. E. J.; Dyer, D. L.; Naylor-Olsen, A. M.; Vacca, J. P.; Gardell, S. J.; Lewis, S. D.; Lucas Jr., B. J.; Lyle, E. A.; Lynch Jr., J. J.; Mulichak, A. M. *Bioorg. & Med. Chem. Lett.* **1997**, *7*, 1497. Tamura, S. Y.; Semple, J. E.; Reiner, J. E.; Goldman, E. A.; Brunck, T. K.; Lim-Wilby, M. S.; Carpenter, S. H.; Rote, W. E.; Oldeshulte, G. L.; Richard, B. M.; Nutt, R. F.; Ripka, W. C. *ibid.* **1997**, *7*, 1543.
6. Fu, J.-min.; Castelhano, A. L. *Bioorg. & Med. Chem. Lett.* **1998**, *8*. in press.
7. (a) Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Snieckus, V. *Chem. Rev.* **1990**. *90*, 879. (c) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
8. Echavarren, A. M.; Stille, J. K.; *J. Am. Chem. Soc.* **1987**, *119*, 5478.
9. (a) Suzuki, A.: *J. Org. Chem.* **1993**, *58*, 2201. (b) Fu, J-M.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665. (c) Huth, A.; Beetz, I.; Schumann, I. *Tetrahedron* **1989**, *45*, 6679.
10. (a) Superchi, S.; Sotomayor, N.; Miao, G.; Joseph, B.; Snieckus, V. *Tetrahedron Lett.* **1996**, *37*, 6057. (b) Quesnelle, C. A.; Familoni, O. B.; Snieckus, V.; *Synlett* **1994**, 349. (c) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. *Synlett* **1990**, 47.
11. Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C. A.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066.
12. (a) Kang, S.-K.; Yamaguchi, T.; Kim, T.-H.; Ho, P.-S. *J. Org. Chem.* **1996**, *61*, 9082. (b) Anderson, J. C.; Namli, H. *Synlett* **1995**, 765. (c) Genet, J. P.; Linquist, A.; Blart, E.; Mouries, V.; Savignac, M. *Tetrahedron Lett.* **1995**, *36*, 1443. (d) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395. (e) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715.
13. Non-aqueous couplings of organohalides with organoborons were explored by Suzuki and co-workers (a) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221. (b) Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008.
14. Typical cross coupling experimental procedure for preparation of **5c**: In a 20 mL borosilicated vial, the mixture of 1-diisopropyloxyphosphorylmethyl-4-trifluoro-methanesulfonyloxy-2-pyridone (0.169 g, 0.40 mmol), tetrakis(triphenylphosphine)- palladium(0) (0.046 g, 0.04 mmol), 3-chlorophenylboronic acid (0.069 g, 0.44 mmol) and potassium carbonate (0.22 g, 1.60 mmol) in tetrahydrofuran-dimethylacetamide (1:1, 4.00 mL) was shaken on J-KEM shaker for 48 hr and then filtered with ethyl acetate as the washing solvent. The filtrate was concentrated *in vacuo* to dryness and the residue was subjected to preparative thin layer chromatography (ethyl acetate) to give 0.14 g (91%) of 1-diisopropyloxyphosphorylmethyl-4-(3-chlorophenyl)-2-pyridone (**5c**) as colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.28 (s, 3H), 1.29 (s, 3H), 1.32 (s, 3H), 4.39-4.45 (d, J = 13.0 Hz, 2H), 4.64-4.80 (m, 2H), 6.37-6.42 (dd, J = 2.0, 7.2 Hz, 1H), 6.73-6.74 (d, J = 2.0 Hz, 1H), 7.35-7.42 (m, 3H), 7.52 (s, 1H), 7.55-7.59 (d, J = 7.2 Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.7, 23.8, 23.9, 24.0, 41.1, 44.2, 72.0, 72.2, 105.3, 117.1, 124.9, 126.9, 129.5, 130.3, 135.0, 137.9, 139.2, 150.4, 161.8; IR (film) υ

981, 1102, 1199, 1239, 1346, 1592, 1660, 2933, 2978 cm^{-1}; MS (ES): 386.0 (M^++1), 384.0 (M^++1).

15. Szardenings, A. K.; Gordeev, M. F.; Patel, D. V. *Tetrahedron Lett.* **1996**, *37*, 3635.

16. Biaryl phosphonic acids have been shown to inhibit phosphatases, see Montserat, J.; Chen. L.; Lawrence, D. S.; Zhang, Z.-Y. *J. Biol. Chem.* **1996**, *271*, 7868.

17. (a) Jackson, R. F. W.; Wishart, N.; Wythes, M. J. *Synlett* **1993**, 219. (b) Jackson, R. F. W.; Wishart, N.; Wood, A.; James, K.; Wythes, M. J. *J. Org. Chem.* **1992**, *57*, 3397. (c) Dunn, M. J.; Jackson, R. F. W.; Stephenson, G. R. *Synlett* **1992**, 905. (d) Jackson, R. F. W.; Wishart, N.; Wythes, M. J. . *J. Chem. Soc., Chem. Commun.* **1992**, 1587. (e) Dunn, M. J.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1992**, 319. (f) Jackson, R. F. W; Wood, A.; Wythes, M. J. *Synlett* **1990**, 735. (g) Jackson, R. F. Wythes, M. J.; W; Wood, A. *Tetrahedron Lett.* **1989**, *30*, 5941. (h)Jackson, R. F. W.; James, K.; Wythes, M J.; Wood, A. *J. Chem. Soc., Chem. Commun.* **1989**, 644.

18. (a) Walker, M. A.; Kaplita, K. P.; Chen, T.; King, H. D. *Synlett* **1997**, 169. (b) Jung, M. E.; Starkey, L. S. *Tetrahedron* **1995**, *53*, 8815. (c) Smyth, M. S.; Burke, Jr., T. R. *Tetrahedron Lett.* **1994**, *35*, 551.

19. Other palladium catalysts investigated and yields obtained were: $Pd_2(dba)_3/AsPh_3$ (25%); $Pd_2(dba)_3CHCl_3/AsPh_3$ (21%); $Pd_2(dba)_3$/ P(2-furyl)$_3$ (14%); $Pd(PPh_3)_4$ (15%); $PdCl_2(o\text{-}tol_3P)_2$ (7%); $Pd_2(dba)_3$/dppf (0%).

20. Data for compound **13**: m.p. 75-77^oC; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.31 (s, 3H), 1.41 (s, 9H), 2.74-3.01 (m, 2H), 4.30-4.38 (dd, J = 3.6, 12.8 Hz, 2H), 4.54-4.74 (m, 3H), 5.01-5.05 (d, J = 7.8 Hz, 1H), 5.15 (s, 2H), 5.86-5.89 (d, J = 6.6 Hz, 1H), 6.32 (s, 1H), 7.26-7.37 (m, 6H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.7, 23.8, 23.9, 24.0, 28.2, 37.6, 40.9, 44.1, 53.1, 67.5, 72.0, 72.2, 77.3, 80.4, 107.6, 120.3, 128.7, 135.0, 137.3, 149.5, 155.1, 161.6, 171.1; IR (film) υ 986, 1165, 1243, 1365, 1597, 1665, 1711, 1745, 2931, 2977 cm^{-1}; MS (ES): 551 (M^++1), 495.